SUPPORT FOR THE AMENDMENTS

Applicants have amended Claims 24, 32, and 39 for clarity and to recite that the composition is in the form of a solution and said antioxidant is present in an amount of 0.2 % to 20% by weight, based on the weight of said composition. Support for these amendments can be found, *e.g.*, at page 13, lines 12-23, as far as the concentration of the antioxidant is concerned, and at page 14, line 11, with regard to the fact that the composition is in the form of a solution. Dependent Claims 25-31, 33-38, and 40-45 have been amended for clarity and to properly depend from the amended independent claims. Applicants have also added new Claims 46-48. Support for new Claims 46-48 can be found on page 13, lines 20-23, of the specification.

No new matter is believed to have been added by these amendments. Claims 24-48 are active in this application.

REMARKS

Present Claims 24-31 and 46 relate to pharmaceutical compositions which comprise a corticosteroid, a propellant, a cosolvent, and an antioxidant, wherein said composition is in the form of a solution and said antioxidant is present in an amount of 0.2 % to 20% by weight, based on the weight of said composition.

Present Claims 32-38 and 47 relate to pressurized metered dose inhalers which comprise a container equipped with a metering valve and containing a pressurized aerosol composition comprising a corticosteroid, a propellant, a cosolvent, and an antioxidant, wherein said composition is in the form of a solution and said antioxidant is present in an amount of 0.2 % to 20% by weight, based on the weight of the composition.

Present Claims 39-45 and 48 relate to methods for the treatment of a bronchial disorder comprising administering a pharmaceutical aerosol composition comprising a corticosteroid, a propellant, a cosolvent, and an antioxidant, wherein said composition is in the form of a solution and said antioxidant is present in an amount of 0.2 % to 20% by weight, based on the weight of the composition.

The inventors have discovered that the presently claimed compositions, pressurized metered dose inhalers, and methods are particularly effective for the treatment of bronchial disorders. The cited references contain no disclosure or suggestion of the presently claimed compositions, pressurized metered dose inhalers, or methods. Accordingly, these references cannot affect the patentability of the present claims.

The rejection of Claims 24, 28-36, and 39-43 under 35 U.S.C. § 102(e) in view of U.S. Patent No. 6,131,566 (Ashurst et al.); the rejection of Claims 24, 28-36, and 39-43 under 35 U.S.C. § 102(e) in view of U.S. Patent No. 5,891,419 (Cutie); the rejection of Claims 24, 28-36, and 39-43 under 35 U.S.C. § 102(e) in view of U.S. Patent No. 5,776,433 (Tzou et al.); the rejection of Claims 25-27, 37, 38, 44, and 45 under 35 U.S.C. § 103(a) in view of Ashurst et al. in view of U.S. Patent No. 4,584,320 (Rubin); the rejection of Claims 25-27, 37, 38, 44, and 45 under 35 U.S.C. § 103(a) in view of Cutie in view of Rubin; the rejection of Claims 24-45 under the judicially-created doctrine of obviousness-type double patenting in view of Claims 1-29 of U.S. Patent No. 6,713,047 in view of Rubin; the provisional rejection of Claims 24-25 under the judicially-created doctrine of obviousness-type double patenting in view of Claims 11-14, 16-26, 28-32, 48, and 49 of copending U.S. Patent Application Serial No. 10/612,072 (US 20040096399); and the provisional rejections of Claims 24-25 under the judicially-created doctrine of obviousness-type double patenting in view of the claims of

copending U.S. Patent Application Serial Nos. 10/275,891 (US 20030190289), 10/435,032 (US 20030206870), 10/435,354 (US 20030190287), and 10/766,857 (US 20040184993) are respectfully traversed.

Ashurst et al. discloses the use of a metered dose inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers for dispensing a drug formulation comprising albuterol (salbutamol) or a salt thereof to reduce or essentially eliminate the problem of adhesion or deposition of the drug to the inner surfaces of the can. The formulation is in the form of a suspension of a finely divided powder of the drug in the propellant.

Therefore Ashurst et al. deals with the specific problem of the adhesion of particles of albuterol (a phenylalkylamino β2-agonist) suspended in the propellant, to the walls of the can (*see, e.g.*, col. 1, lines 20-22, 51,60-63; and col. 6, lines 47 and 55-60).

A polar cosolvent, such as ethanol, may be included in the formulation, either as the only excipient or in addition to other excipients. Suitably, in this case, the formulation will contain only a little amount of ethanol, from 0.01 to 5% w/w, preferably 0.1 to 5% w/w, *e.g.*, about 0.1 to 1% w/w based on the propellant (*see*, col. 3, lines11-18). This disclosure is directly at odds with the present invention wherein the drug is a corticosteroid ***in solution*** in the propellant and the cosolvent (*e.g.*, ethanol) is used to dissolve the drug in the propellant (*see*, for example, at page 12 lines 2-7 and Tables 1, 2 , 4, to 8 wherein examples of corticosteroid compositions in the form of a solution are reported, containing ethanol in an amount from about 8% to about 15%).

From the disclosure by Ashurst et al., it is clear that ethanol is not a cosolvent as used in the present invention.

Furthermore, Ashurst et al., despite a generic statement that excipients may be contained in the albuterol formulation and that the excipients include antioxidants, lacks disclosure on specific antioxidants and the relevant amounts.

The claims of the present application, as amended, now specify that the antioxidant is present in an amount of 0.2% to 20% w/w, preferably 1% to 2% w/w. The addition of an antioxidant, as a low volatility component, allows the modulation of the size of the liquid particles delivered on actuation of the inhaler, to provide aerosol compositions based on an HFA propellant, having the same characteristics of the old CFC compositions which they replace (*see*, at page 8, lines 1-19 and 25-29).

Therefore, there would be no reason for the skilled in the art to turn to Ashurst et al. to solve the problem of the preparation of an aerosol composition of a corticosteroid in the form of a solution in an HFA propellant and a cosolvent, further containing an antioxidant in a well defined amount.

Cutie discloses aerosol formulations for oral inhalation containing flunisolide ***dispersed*** in HFC 134a and/or HFC 227 (*see*, Abstract). The aerosol formulations disclosed by Cutie are free of CFCs and surfactants, and contain little or no ethanol. In regard to the small amounts of ethanol, Cutie discloses, at column 4, lines 5-16, that ethanol is present to ***prevent dissolution*** of the flunisolide. However, this disclosure is directly at odds with the present invention wherein a cosolvent (*e.g.*, ethanol) is used to *dissolve* the active ingredient in the propellant (*see*, for example, pages 10-12 and the Examples). From this disclosure in Cutie, it is clear that ethanol is not a cosolvent as used in the present invention as its function in the aerosol formulation is substantially different from that of a cosolvent, which is presently claimed.

Applicants submit the following additional reasons why the presently claimed invention is not obvious in view of Cutie. In the present claims, the composition is required to exist in the form of a solution. Therefore, Applicants submit that the disclosure of Cutie falls far short of disclosing or suggesting the claimed invention.

Further, Cutie widely expounds the difficulties inherent in the preparation of aerosol formulations with HFA propellants (*see*, column 1, lines 44-60) and discourages the use of a co-solvent in solution formulations, to enhance drug dissolution, in that "this practice may have the disadvantage of decreasing the fraction of the metered dose which may be inhaled and contributing to particle size growth" (*see*, column 1, lines 60-65). As such, Cutie favors avoiding that which is presently claimed.

Applicants note that MPEP §2141.02 states: "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). In view of the disclosure at column 4, lines 5-16, Cutie teaches away from the inclusion of ethanol as a cosolvent and/or the complete dissolution of the corticosteroid in the propellant vehicle. Therefore, the disclosure in Cutie fails to render the present invention obvious.

Additionally, in spite of the general disclosure that the drug may be dissolved in the propellant, Cutie is specifically directed to suspension formulations that require a sugar as a necessary component of the formulation acting as a dispersant. More specifically Cutie discloses flunisolide aerosol formulations wherein flunisolide is dispersed in the propellant (*see*, column 3, fine 35) and wherein the ethanol merely aids in dispersing the drug (*see*, column 4, line 5). The formulations may contain ethanol, but

when ethanol is present it comprises less than 5% of the formulation (*see*, column 5, lines 5 and 6). On the contrary, Example 3 of the present invention shows that at least 13% w/w ethanol is necessary to solubilize 12 mg of budesonide in the formulation. Therefore, Cutie fails to achieve yet another limitation of the claimed invention – complete dissolution of budesonide. Furthermore, Cutie lacks disclosure on canister specifics and does not account for the chemical stability of the active ingredient.

Tzou et al. discloses aerosol compositions comprising flunisolide, ethanol and HFA propellants and discloses that certain excipients, *e.g.*, certain surfactants, flavoring agents, and/or water are beneficial to some embodiments of the invention. In particular the chemical stability of certain formulations of flunisolide is enhanced by the presence of water, sorbitan trioleate and cetylpyridinium chloride (see, col. 3, lines 16-28). It is also stated that conventional aerosol canisters can be used for keeping the composition and that certain containers enhance the chemical stability of certain formulations and/or minimize the absorption of flunisolide onto the container walls. It is suggested that the composition be preferably kept within a glass aerosol vial or an aluminium aerosol vial having an interior formulation chamber coated with a resin that is inert to flunisolide and preferably does not *absorb* flunisolide from the formulation, like epoxy resins (*e.g.*, epoxy phenol resins and epoxy urea formaldehyde resins; see, col. 4, lines 1-14).

Tzou et al. also discloses that flunisolide has been previously provided in the form of a nasal formulation in a solution of propylene, polyethylene glycol 3350, citric acid, sodium citrate, butylated hydroxyanisole, edetate disodium, benzalkonium chloride and purified water.

Rubin is directed to a method and composition for the prevention and treatment of

asthmatic attacks and bronchial spasms by the use of a natural compound represented by 8,11,14,17-eicosatetraenoic acid (ETA) or a pharmaceutically acceptable salt or ester thereof. The compound may be administered by direct oral or nasal inhalation. For such a kind of administration, the use of a pressurized inhaler with known propellants, such as trichlorofluoromethane and dichlorodifluoromethane, with the optional presence of dispersing agents, all as is well known in the art, is generically suggested (*see*, column 3, lines 63-68). Therefore, Rubin is concerned with suspension formulations in the old CFC propellants. Moreover, the formulations of Rubin do not contain a cosolvent.

Since ETA is a polyunsaturated fatty acid, easily subject to oxidation, Rubin recommends adding to any pharmaceutical composition containing ETA a suitable antioxidant. In any case, Rubin does not disclose aerosol compositions in the form of a solution containing a corticosteroid dissolved in an HFA propellant by the aid of a cosolvent and particularly of ethanol.

Therefore from the teaching of Rubin, the skilled in the art would not derive any information about the possibility of successfully formulating a corticosteroid as a solution in the new HFA propellants, which have chemico-physical characteristics and solubilizing properties completely different from the CFC propellants that they replace.

In the Office Action, it is asserted that it would have been obvious to a person skilled in the art at the time the invention was made, given the general formulations of Ashurst et al. to have looked to the art, namely to Rubin, for specific antioxidants suitable for inhalation preparations such as tocopherol and ascorbyl palmitate , with the reasonable expectation of successfully preparing a stable and efficient formulation for treating respiratory disorders. Applicants respectfully disagree.

Both Ashurst et al. and Rubin are concerned with compositions in the form of a suspension, containing a specific drug, albuterol in the first case, and a polyunsaturated fatty acid (ETA) in the second one. The technical problem in Ashurst et al. is to avoid adhesion of the particles of albuterol to the internal walls of the can. The compositions of Rubin are suspension based on a CFC propellant, with the optional presence of a dispersing agent. Thus, Rubin does not foresee at all the presence of a cosolvent.

Therefore, there would be no motivation for one skilled in the art to look at these documents of the prior art to prepare a composition of a corticosteroid in the form of a solution in an HFA propellant, utilizing a cosolvent to solubilize the active ingredient in the propellant and a specific amount of an antioxidant to provide an aerosol MDI pharmaceutically and clinically equivalent to previous CFC MDIs (see, page 8 lines17-19, of the present specification).

Analogously there would be no motivation for the skilled in the art to combine the disclosure of Cutie with Rubin.

In fact, Cutie discloses flunisolide aerosol formulations wherein flunisolide is dispersed in the propellant (*see*, column 3, line 35) and wherein the ethanol merely aids in dispersing the drug (*see,* column 4, line 5). Cutie explicitly expounds the difficulties inherent in the preparation of aerosol formulations with HFA propellants (*see*, column 1, lines 44-60) and discourages the use of a co-solvent in solution formulations, to enhance drug dissolution, in that "this practice may have the disadvantage of decreasing the fraction of the metered dose which may be inhaled and contributing to particle size growth" (*see*, column 1, lines 60-65).

In contrast, in the present claims, the corticosteroid is required to be completely dissolved in the propellant. This is neither disclosed nor suggested by the combined

disclosures of Rubin and Cutie.

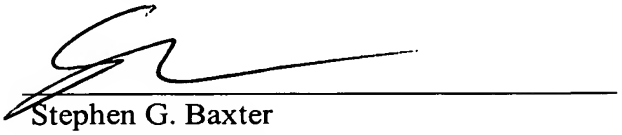
For all of these reasons, the rejections based on the prior art under 35 U.S.C. §§ 102 and 103 are improper and should be withdrawn.

As for the double patenting rejections and the provisional double patenting rejections, Applicants submit that the claims of none of the cited patents or copending applications, either taken by themselves or in combination with Rubin, remotely suggest: (1) a pharmaceutical composition which comprises a corticosteroid, a propellant, a cosolvent, and an antioxidant, in which the composition is in the form of a solution and the antioxidant is present in an amount of 0.2 % to 20% by weight, based on the weight of said composition; (2) a pressurized metered dose inhaler which contains such a composition; or (3) a method of treating a bronchial disorder by administering such a composition. Accordingly, all of the double patenting rejections and provisional double patenting rejections should be withdrawn.

Applicants submit that the present application is in condition for allowance, and early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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